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(57) Abstract

Potentiating agents which enhance the efficacy of antineoplastic agents are disclosed. The potentiating agents disclosed are α-aryl-4-substituted piperidinoalkanol derivatives such as terfenadine, 11-(4-piperi-dylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridines such as Loratadine, and N-heterocyclyl-4-piperidinamines wherein said heterocyclic radical is an optionally substituted 1H-benzimidazol-2-yl or 3H-imidazo[4,5-*b*]pyridin-2-yl radical, such as astemizole.

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AGENTS FOR POTENTIATING THE EFFECTS OF ANTITUMOR AGENTS AND COMBATING MULTIPLE DRUG RESISTANCE

Field of the Invention

The present invention relates to the use of α-aryl-4-substituted piperidinoalkanol derivatives such as terfenadine, 11-(4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2- b]-pyridines such as Loratadine, and N-heterocyclyl-4-piperidinamines wherein said heterocyclic radical is an optionally substituted 1H-benzimidazol-2-yl or 3H-imidazo[4,5-*b*]pyridin-2-yl radical compound, such as astemizole, as adjuvant chemotherapy for neoplasias resistant to multiple drugs. The present invention also relates to the use of such compounds as agents for enhancing the therapeutic effect of multiple antitumor agents.

Background of the Invention

Complete cures of various tumors like leukemias, lymphomas and solid tumors by the use of chemotherapeutic agents are rare because of heterogeneous sensitivity of tumor cells to each antitumor agent. Cancer chemotherapy also fails because of intrinsic resistance of tumors to multiple drug therapies. In other cases, a tumor may become resistant to the antitumor agents used in a previous treatment. The therapeutic effects of these agents are then eliminated. An even graver problem is that recurrent cancers are resistant not only to the cancer suppressants used in previous treatments, but also manifest resistance to

other antitumor agents, unrelated to the agent used previously either by chemical structure or by mechanism of action. These phenomenon are collectively referred to multiple drug resistance (mdr) and contribute widely to cancer treatment failures in the clinic.

The major documented cause of multiple drug resistance is overexpression of a membrane glycoprotein (the multiple drug transporter) responsible for pumping structurally diverse antitumor drugs from cells. See D. Houseman et al., A Molecular Genetic Approach to the Problem of Drug Resistance in Chemotherapy, 504-517 (1987) (Academic Press, Inc.); R. Fine and B. Chabner, Multidrug Resistance, in Cancer Chemotherapy 8, 117-128 (H. Pinedo and B. Chabner eds. 1986).

Tumor cells expressing elevated levels of the multiple drug transporter accumulate far less antitumor agents intracellularly than tumor cells having low levels of this enzyme. The degree of resistance of certain tumor cells has been documented to correlate with both elevated expression of the drug transporter and reduced accumulation of antitumor drugs. See M. Gottesman and I. Pastan, J. Biol. Chem. 263, 12163 (1988); see also A. Fojo et al., Cancer Res. 45, 3002 (1985). This form of multiple drug cross-resistance involves agents derived from natural products, such as the vinca alkaloids, the anthracyclines, the epipodophyllotoxins, actinomycin D and plicamycin. See I. Pastan and M. Gottesman, New England J. Med. 1388, 1389 Table 1 (May 28, 1987).

Adenocarcinomas derived from adrenal, kidney, liver, small intestine, and colon tissue are notorious for exhibiting inherent cross-resistance to chemically unrelated chemotherapeutic agents. See M. Gottesman and I. Pastan, supra at 12165; see also A. Fojo et al., J. Clin. Oncol. 5, 1922 (1987). These tissues normally express higher levels of the multidrug transporter. Other tumors documented to express high levels of the multidrug transporter include pancreatic, carcinoid,

chronic myelogenous leukemia in blast crisis, and non-small cell lung carcinoma. Tumors documented to initially be drug-sensitive but to then become drug resistant include neuroblastoma, pheochromocytoma, multiple myeloma, acute lymphocytic leukemia in adults, acute nonlymphocytic leukemia in adults, nodular poorly differentiated lymphoma, breast cancer and ovarian cancers. It is estimated by the National Cancer Institute that approximately half a million tumor samples a year will be drug resistant because of aberrant levels of expression of the multidrug transporter. See L. Goldstein et al., Expression of Multidrug Resistance Gene in Human Cancers, J. National Cancer Institute 81, 116 (1988).

Elevated levels of expression of the mdr drug transporter in these tumors would lead to reduced levels of antitumor agents in the tumor and would suppress their chemotherapeutic efficacy. Tumors having elevated levels of the multiple drug transporter would require therapeutic doses of cancer suppressants far in excess of tumors exhibiting lower levels of the mdr drug transporter. Agents that inhibit the active efflux of antitumor agents by the drug transporter or agents that potentiate the efficacy of chemotherapeutic agents would enhance the activity of various antitumor agents on tumor cells. As a result of the present inventors' study, it has unexpectedly been found that when the potentiating agents disclosed herein are used together with an antitumor agent, they can remarkably enhance the therapeutic effect of the antitumor agent, and that multiple drug resistance is resolved by increasing the susceptibility to actinomycin D.

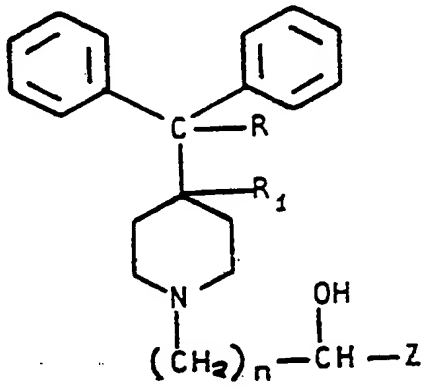
A number of agents used clinically as calcium channel-blockers, calmodulin inhibitors and antiarrhythmic agents promote the activity of antitumor agents against resistant tumor cells, see Tsuruo et al., Cancer Res. 44, 4303 (1984); 43, 2267 (1983). Verapamil,

caroverine, clomipramine, trifluoperazine, prenylamine, diltiazem, nicardipine, and quinidine enhance the activity of antitumor agents against resistant sublines of murine leukemia cells. Most agents potentiating the activity of antitumor agents are calcium antagonists, and the serious cardiotoxicities that arise during treatment have limited their clinical usefulness. While the inventors do not wish to be bound by any theory of operation for the present invention, it is noted that the potentiating agents disclosed herein are not known to have calcium antagonism, but do elevate the intracellular concentration of antineoplastic drugs in tumor cells overexpressing the multiple drug transporter. Sensitization of drug resistant tumors and elevation of intracellular antitumor drug concentrations probably occur by a mechanism different from calcium antagonism.

Summary of the Invention

An object of the present invention is to provide an agent for enhancing the therapeutic effect of an antineoplastic agent by administering to a subject harboring a tumor a compound of Formula (I) below or a pharmaceutically acceptable acid addition salt thereof

(I)



wherein

R represents hydrogen or hydroxy;

R_1 represents hydrogen; or

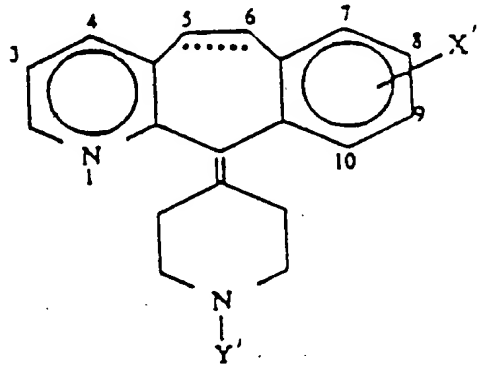
R and R_1 taken together form a second bond between the carbon atoms bearing R and R_1;

n is a positive whole integer of from 1 to 3;

Z represents thienyl, phenyl or substituted phenyl wherein the substituents on the substituted phenyl are selected from a halogen atom, such as chlorine, fluorine, bromine, or iodine, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, a di(lower)alkylamino group, or a saturated monocyclic heterocyclic group such as pyrrolidino, piperidino, morpholino, or N-(lower) alkylpiperazino and may be attached at the ortho, meta, or para positions of the phenyl ring.

Included in the scope of this invention are the individual optical isomers of the compounds of Formula I.

A second object of the present invention is to provide an agent for enhancing the therapeutic effect of an antineoplastic agent by administering to a subject harboring a tumor a compound of Formula (II) below or a pharmaceutically acceptable salt thereof



(II)

wherein the dotted line represents an optional double bond and wherein the numbering system used herein is illustrated. In Formula (II), X' is hydrogen or halo and Y' is hydrogen, substituted carboxylate or substituted

sulfonyl, for example Y' is H, -COOR', or SO_2R', with the proviso that when Y' is -COOR', R' is C1 to C12 alkyl, substituted C1 to C12 alkyl, phenyl, substituted phenyl, C7 to C12 phenyl alkyl, C7 to C12 phenyl alkyl wherein the phenyl moiety is substituted or R' is -2,-3, or -4 piperidyl or N-substituted piperidyl wherein the substituents on said substituted C1 to C12 alkyl are selected from amino or substituted amino and the substituents on said substituted amino are selected from C1 to C6 alkyl, the substituents on said substituted phenyl and on said substituted phenyl moiety of the C7 to C12 phenyl alkyl are selected from C1 to C6 alkyl and halo, and the substituent on said N- substituted piperidyl is C1 to C4 alkyl; and with the proviso that when Y' is SO_2R', R' is C1 to C12 alkyl, phenyl, substituted phenyl, C7 to C12 phenyl alkyl, C7 to C12 phenyl alkyl wherein the phenyl moiety is substituted, wherein the substituents on said substituted phenyl and said substituted phenyl moiety of the C7 to C12 phenyl alkyl are selected from C1 to C6 alkyl and halo.

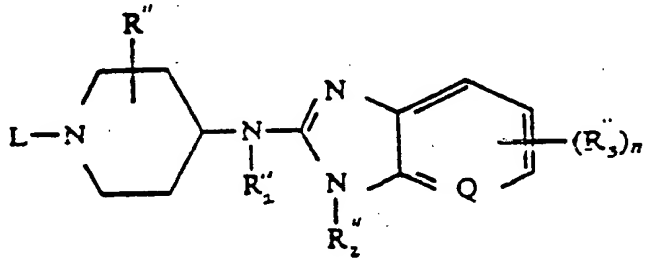
In a preferred embodiment of the potentiating agent according to Formula (II), Y' is -COOR' and R' is C1 to C6 alkyl or substituted alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl or -2, -3 or -4 piperidyl or N-substituted piperidyl. When R' is substituted alkyl, R' is substituted with amino or with substituted amino. The substituents on said substituted amino are C1 to C6 alkyl. The substituents on the aforementioned substituted phenyl and on the phenyl moiety of the substituted aralkyl are preferably C1 to C6 alkyl or halo.

In a second preferred embodiment of the potentiating agent of Formula (II), Y' is SO_2R' and R' is C1 to C6 alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl, wherein the substituents on said substituted phenyl and on the phenyl moiety of the substituted aralkyl are C1 to C6 alkyl or halo.

In a third preferred embodiment of the potentiating agenty of Formula (II), Y' is H.

The aforementioned alkyl groups of the compound of Formula II may be linear, branched or cyclic or may contain both cyclic and linear or cyclic and branched moieties. Halo may be fluoro, chloro, bromo or iodo.

A third object of the present invention is to provide an agent for enhancing the therapeutic effect of an antineoplastic agent by administering to a subject harboring a tumor a compound represented by the formula:



(III)

and the pharmaceutically acceptable acid addition salts thereof, wherein:

R'' is a member selected from the group consisting of hydrogen and lower alkyl;

R_1'' is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R_2'' is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono and diaryl(lower alkyl);

R_3'' is a member independently selected from the group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl;

n'' is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and

L is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano,

hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; lower alkenyl; aryllower alkenyl; cycloalkyl, being optionally substituted with a cyano and/or an aryl group; 1-(aryllower alkyl)-1H-benzimidazol-2-yl; and a radical of the formula $Z''-C_mH_{2m}-$, wherein

m is an integer of from 1 to 6 inclusive; and

Z'' is a member selected from the group consisting of 4,5-dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted in its 4-position by an aryl radical or a lower alkyl radical; 2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzodioxin-6-yl; 2,3-dihydro-2-oxo- 1H-benzimidazol-1-yl; 2,3-dihydro-3-oxo-4H-benzoxazin-4-yl;(10,11-dihydro-5H-di-benzo[a,d]cyclohepten-5-ylidene)methyl; 4-morpholinyl; 1-piperidinyl; 1-pyrrolidinyl; a radical of the formula $T-N(R_4'')-$, wherein

R_4'' is a member selected from the group consisting of hydrogen, lower alkyl and aryllower alkyl; and

T is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, 1H-benzimidazol-2-yl; and

a radical of the formula

$$W - \overset{O}{\overset{\|}{C}} - (X'')_s - \qquad \text{(VIII)}$$

wherein

s is the integer 0 or 1;

X'' is a member selected from the group consisting of O and $-N(R_5'')-$, said R_5 being a member selected from the group consisting of

hydrogen, lower alkyl, aryllower alkyl, lower alkanoyl and aroyl; and

W is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, amino, arylamino, mono- and di(lower alkyl)amino, mono- and di(aryllower alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

wherein aryl, as used in the foregoing definitions of Formula (II), is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono-and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substitutents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono-and di(lower alkyl)amino, lower alkanoyl, a radical of the formula $R_6''-C_pH_{2p}-O-$, wherein

p is an integer of from 1 to 6 inclusive; and

R_6'' is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and a radical of the formula $R_7''-O-$, wherein

R_7'' is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl,

aminocarbonyl, phenylaminocarbonyl, mono- and di(lower alkyl)aminocarbonyl;

wherein said phenyl in the definition of said R_7'' may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy; and

wherein said aroyl in the definition of said L represents arylcarbonyl wherein said aryl is as defined hereabove.

As used in the foregoing definitions the term "lower alkyl" is meant to include straight and branch chained hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like; the term "alkyl" as used in the definition of R_2'' includes straight and branch chained hydrocarbon radicals having from 1 to 10 carbon atoms, such as, for example, the above-indicated lower alkyls and higher homologs such as heptyl, octyl, nonyl and decyl; the term "lower alkenyl" refers to straight alkenyl radicals having from 3 to 6 carbon atoms wherein the unsaturation is preferably located at the beta -position but may also be located at the gamma, delta, or epsilon -position such as for example, 2-propenyl, 2-butenyl, 3-pentenyl, 2-hexenyl and the like; the term "cycloalkyl" refers to cyclic hydrocarbon radicals having from 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and the term "halo" is generic to fluoro, chloro, bromo and iodo.

Another aspect of the present invention is a method of increasing the sensitivity of a tumor to an antineoplastic agent when the tumor is resistant to the antineoplastic agent by administering to the subject harboring the resistant tumor a potentiating agent (i.e., a compound of Formula (I), (II) or (III)) concurrently with an antineoplastic agent. Resistance to the antineoplastic agent may (a) be an intrinsic property of

the tumor or (b) develop in response to prior treatment with the same antineoplastic agent or another antineoplastic agent capable of selecting for multi-drug resistance.

An additional aspect of the present invention is a method of selectively inhibiting the growth of tumor cells in a subject in need of such treatment by concurrently administering to the subject an antineoplastic agent and a potentiating agent. The potentiating agent is administered in an amount effective to (a) reduce the amount of the antineoplastic agent required to achieve the same growth inhibiting effect on the tumor cells by the antineoplastic agent achieved without the concurrent administration of the potentiating agent; or (b) inhibit the development of multiple drug resistance in the tumor cells after treatment with the antineoplastic agent over time. Another aspect of the present invention is a method of inhibiting multiple drug resistance in a subject in need of such treatment by administering the subject a potentiating agent in an amount effective to combat multiple drug resistance.

Also disclosed is the use of the compounds of Formula (I), Formula (II), and Formula (III) above for the manufacture of a medicament for the inhibition of multiple drug resistance in tumors.

Detailed Description of the Invention

It can be seen from the Formula (I) above that compounds included therein may be 4-diphenylmethyl-piperidine derivatives as represented by the following Formula (IV), 4-(α-hydroxy-α-phenylbenzyl)piperidine derivatives as represented by the following Formula (V), or 4-diphenylmethylenepiperidine derivatives as represented by the following Formula (VI).

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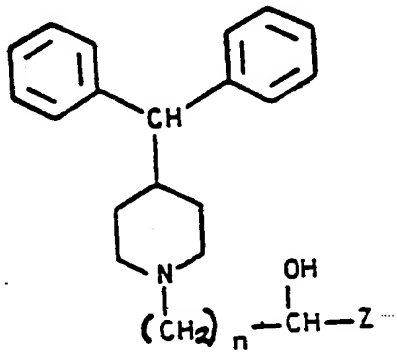
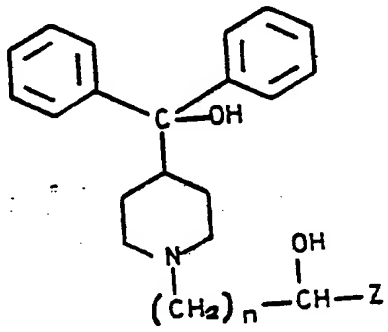
(IV)



(V)



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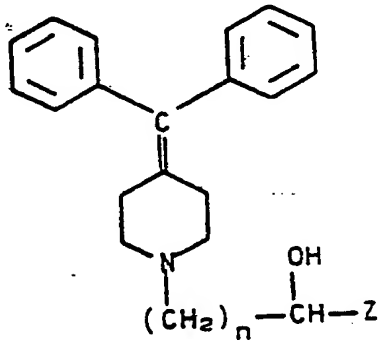
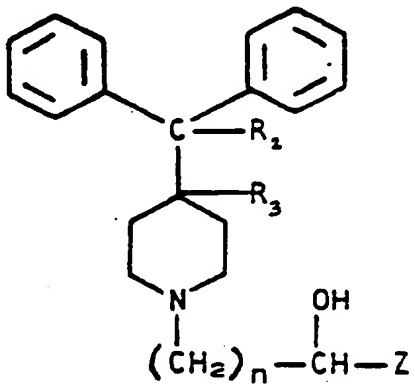


In the above Formulas (IV), (V) and (VI), n and Z have the same meanings as defined for Formula (I) hereinbefore.

The term lower alkyl as used in describing the compounds of according to Formula (IV), (V), and (VI) is taken to mean a straight or branched alkyl chain of from 1 to 4 carbon atoms. As examples of lower alkyl groups that may be present in the compounds for Formulas (I), (IV), (V) and (VI) as a straight or branched lower alkyl substituent, or in the di(lower)alkylamine substituent, or in the N-(lower)alkylpiperazine substituent on Z when Z represents a substituted phenyl there may be mentioned,

methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl and tert-butyl.

The preferred compounds of this potentiating agent are those of general Formulas (V) and (VI) wherein n and Z have the meanings defined hereinbefore, and may be represented by the following Formula (VII).



(VII)

In the above Formula (VII),

R_2 represents hydroxy, and

R_3 represents hydrogen, or

R_2 and R_3 taken together form a second bond between the carbon atoms bearing R_2 and R_3; and

n and Z are as defined hereinbefore.

The more preferred compounds of this invention are those of general Formula (VII) wherein n is equal to 3.

The following compounds are exemplary of formula (I) above:

(A) α-(p-tert-butylphenyl)-4-(α-hydroxy-α-phenylbenzyl)-1-piperidinebutanol (or "terfenadine"; or "α-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol");

(B) α-(p-fluorophenyl)-4-(α-hydroxy-α-phenylbenzyl)-1-piperidinebutanol;

(C) 4-(diphenylmethyl)-α-(p-fluorophenyl)-1-piperidinebutanol;

(D) 4-(diphenylmethyl)-α-(p-ethoxyphenyl)-1-piperidinepropanol;

(E) 4-(α-hydroxy-α-phenylbenzyl)-α-(p-morpholinophenyl)-1-piperidinebutanol;

(F) 4-(diphenylmethylene)-α-(2-thienyl)-1-piperidinebutanol;

(G) 4-(diphenylmethylene)-α-(p-fluorophenyl)-1-piperidinebutanol;

(H) 4-(diphenylmethylene)-α-(p-methoxyphenyl)-1-piperidinebutanol;

(I) 4-(diphenylmethylene)-α-(p-dimethylaminophenyl)-1-piperidinepropanol;

(J) 4-(α-hydroxy-α-phenylbenzyl)-α-phenyl-1-piperidineethanol;

(K) 4-(diphenylmethyl)-α-(p-isopropylphenyl)-1-piperidinebutanol;

(L) 4-(diphenylmethylene)-α-(p-fluorophenyl)-1-piperidinebutanol;

(M) (+)-α-(p-tert-butylphenyl)-4-(α-hydroxy-α-phenylbenzyl)-1-piperidinebutanol;

(N) 4-(α-hydroxy-α-phenylbenzyl)-α-(2-thienyl)-1-piperidinebutanol;

(O) α-(p-bromophenyl)-4-(α-hydroxy-α-phenylbenzyl)-1-piperidinebutanol;

(P) α-(p-bromophenyl)-4-(diphenylmethylene)-1-piperidinebutanol;

(Q) 4-(diphenylmethyl)-α-phenyl-1-piperidinebutanol;

(R) 4-(α-hydroxy-α-phenylbenzyl)-α-phenyl-1-piperidinebutanol;

(S) 4-(α-hydroxy-α-phenylbenzyl)-α-(p-methylphenyl)-1-piperidinebutanol;

(T) α-(p-fluorophenyl)-4-(α-hydroxy-α-phenylbenzyl)-1-piperidinepropanol;

(U) 4-(α-hydroxy-α-phenylbenzyl)-α-(p-piperidinophenyl)-1-piperidinebutanol;

(V) α-(p-dimethylaminophenyl)-4-(α-hydroxy-α-phenylbenzyl)-1-piperidinebutanol;

(W) 4-(α-hydroxy-α-phenylbenzyl)-α-(p-methoxyphenyl)-1-piperidinebutanol;

(X) α-(p-fluorophenyl)-4-(α-hydroxy-α-phenylbenzyl)-1-piperidineethanol;

(Y) α-(p-tert-butylphenyl)-4-(diphenylmethylene)-1-piperidinebutanol;

(Z) 4-(α-hydroxy-α-phenylbenzyl)-α-[p-(N-methylpiperazino)-phenyl]-1-piperidinebutanol;

(AA) 4-(diphenylmethylene)-α-(p-pyrrolidinophenyl)-1-piperidinebutanol; and

(AB) (-)-α-(p-tert-butylphenyl)-4-(α-hydroxy-α-phenylbenzyl)-1-piperidinebutanol.

The compounds of the present invention are known, and are described in U.S. Patent No. 3,878,217, the disclosure of which is incorporated herein by reference. They may be made in the manner described in Pat. No. 3,878,217, or may be prepared by an alkylation reaction of an appropriately substituted piperidine derivative with an omega -haloalkyl aryl ketone derivative in an alcoholic or hydrocarbon solvent in the presence of a base as disclosed in U.S. Pat. No. 3,806,526, the disclosure of which is incorporated herein by reference.

Potentiating agents exemplary of the potentiating agent of Formula (II) include:

(AC) 11-(N-Carboethoxy-4-piperidylidene)-8-chloro-6, 11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b] -pyridine (or ethyl-4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta [1,2b]pyridin-11-ylidene)-1-piperidine carboxylate) (or **Loratadine**);

(AD) 11-(N-Carboethoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

(AE) 11-(N-Carbomethoxy-4-piperidylidene)-6, 11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

(AF) 11-(N-Carbophenoxy-4-piperidylidene)-6, 11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

(AG) 11-(N-Carboisopropoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b] pyridine;

(AH) 11-(N-Carbo-t-butoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

(AI) 11-(N-Methanesulfonyl-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine; and

(AJ) 11-(4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine (or **Descarboethoxyloratadine**).

Compounds (AC) through (AJ) are described in U.S. Patent No. 4,282,233 to Vilani, the disclosure of which is incorporated herein by reference. Compound H is described in J. Hilbert et al., J. Int. Med. Res. 16, 50 (1988), the disclosure of which is also to be incorporated herein by reference. Compound H can be made by following the teachings of Patent No. 4,282,233 in view of procedures and principles known in the art.

Compounds which are potentiating agents exemplary of Formula (III) above and how to make the same are disclosed in U.S. Patent No. 4,219,559, the disclosure of which is incorporated herein by reference. Most preferred is:

(AK) 1-[(4-Fluorophenyl)methyl]-N-[-1-[2-(4-methoxyphenyl)ethyl-4-piperidinyl]-1H-benzimidazol-2-amine (or **"astemizole"**).

A preferred category of multiple drug resistant tumor cells to be treated by the method of the present invention are multiple drug resistant cells characterized by the multidrug transporter - mediated pumping of antineoplastic agents out of the tumor cells. The multidrug transporter protein is described in M. Gottesman and I. Pastan, supra. Thus, tumor cells treated by the present invention are preferably those characterized by (a) the expression of the multidrug

transporter protein at high levels, or (b) the ability to express the multidrug transporter protein upon selection by an antineoplastic agent.

Exemplary of tumor cells which express the multidrug transporter at high levels (intrinsically resistant cells) are adenocarcinoma cells, pancreatic tumor cells, carcinoid tumor cells, chronic myelogenous leukemia cells in blast crisis, and non-small cell lung carcinoma cells.

Exemplary of tumor cells having the ability to express the multidrug transporter protein upon selection by an antineoplastic agent are neuroblastoma cells, pheochromocytoma cells, adult acute lymphocytic leukemia cells, adult acute nonlymphocytic leukemia cells, nodular poorly differentiated lymphoma cells, breast cancer cells and ovarian cancer cells.

A preferred group of tumor cells for treatment in the present invention are the adenocarcinomas, including adenocarcinomas of adrenal, kidney, liver, small intestine and colon tissue, with kidney adenocarcinoma cells particularly preferred.

Preferred antineoplastic agents for use in the present invention are those to which multidrug transporter - mediated multiple drug resistant cells develop resistance. Exemplary of such antineoplastic agents are vinca alkaloids, epipodophyllotoxins, anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, taxol, colchicine, cytochalasin B, emetine, maytansine, and amsacrine (or "mAMSA"). Preferred are vinca alkaloids, epipodophyllotoxins, anthracyclene antibiotics, actinomycin D, and plicamycin.

The vinca alkaloid class is described in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 1277-1280 (7th ed. 1985) (hereafter "Goodman and Gilman"). Exemplary of vinca alkaloids are vincristine, vinblastine, and vindesine.

The epipodophyllotoxin class is described in Goodman and Gilman, supra at 1280-1281. Exemplary of epipodophyllotoxins are etoposide, etoposide orthoquinone, and teniposide.

The anthracycline antibiotic class is described in Goodman and Gilman, supra at 1283-1285. Exemplary of anthracycline antibiotics are daunorubicin, doxorubicin, mitoxantraone, and bisanthrene. Daunorubicin and doxorubicin are preferred.

Actinomycin D, also called Dactinomycin, is described in Goodman and Gilman, supra at 1281-1283. Plicamycin, also called mithramycin, is described in Goodman and Gilman, supra at 1287-1288.

The phrase "concurrently administering," as used herein, means that the antineoplastic agent and the potentiating agent are administered either (a) simultaneously in time (optionally by formulating the two together in a common carrier), or (b) at different times during the course of a common treatment schedule. In the latter case, the two compounds are administered at times sufficiently close for the potentiating agent to enhance the selective growth-inhibiting action of the antineoplastic agent on the tumor cells.

Subjects to be treated by the method of the present invention include both human and animal (e.g., dog, cat, cow, horse) subjects, and are preferably mammalian subjects.

The potentiating agents of Formulas (I), (II), and (III) are administered in an amount effective to enhance the efficacy of the antineoplastic agent. The potentiating agent is preferably administered in a total amount per day of not more than about 50 mg/kg body weight, more preferably not more than about 25 mg/kg, and most preferably not more than about 5 mg/kg. With respect to minimum dose, the potentiating agent is preferably administered in a total amount per day of at least about .01 mg/kg, more preferably at least about .1

mg/kg, and most preferably at least about 1 mg/kg. The potentiating agent may be administered once or several times a day.

As noted above, the compounds of Formulas (I), (II) and (III) may be administered per se or in the form of a pharmaceutically acceptable salt. When used in medicine, the salts of the compounds of Formulas (I), (II) and (III) should be both pharmacologically and pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare the free active compound or pharmaceutically acceptable salts thereof and are not excluded from the scope of this invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluenesulfonic, tartaric, citric, isethionic, methanesulphonic, formic, malonic, succinic, naphthalene-2-sulphonic and benzenesulphonic. Also, pharmaceutically acceptable salts of Formula (II) can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group. Thus, the present invention also provides pharmaceutical formulations, both for veterinary and for human medical use, which comprise one of the potentiating agents of Formulas (I), (II) and (III) together with one or more pharmaceutically acceptable carriers thereof and optionally any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not unduly deleterious to the recipient thereof.

Pharmaceutical formulations of the present invention may optionally include an antineoplastic agent, preferably an agent as described above. Such a formulation is useful for concurrently administering an

antineoplastic agent and the potentiating agent in a method as described above.

The formulations include those suitable for oral, rectal, topical, nasal, ophthalmic or parenteral (including subcutaneous, intramuscular and intravenous) administration. Formulations suitable for oral and parenteral administration are preferred.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the potentiating agent as a powder or granules; or a suspension in an aqueous liquor or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which is optionally mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets comprised of a mixture of the powdered active compound with a suitable carrier may be made by molding in a suitable machine.

A syrup may be made by adding the active compound to a concentrated aqueous solution of a sugar, for example sucrose to which may also be added any

accessory ingredient(s). Such accessory ingredient(s) may include flavorings, suitable preservatives, an agent to retard crystallization of the sugar, and an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol, for example glycerol or sorbitol.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound, which is preferably isotonic with the blood of the recipient.

Nasal spray formulations comprise purified aqueous solutions of the active compound with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes.

Formulations for rectal administration may be presented as a suppository with a suitable carrier such as cocoa butter, or hydrogenated fats or hydrogenated fatty carboxylic acids.

Ophthalmic formulations are prepared by a similar method to the nasal spray, except that the pH and isotonic factors are preferably adjusted to match that of the eye.

Topical formulations comprise the active compound dissolved or suspended in one or more media such as mineral oil, petroleum, polyhydroxy alcohols or other bases used for topical pharmaceutical formulations. The addition of other accessory ingredients, vide infra, may be desirable.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

The following Examples are provided to illustrate the present invention, and should not be construed as limiting thereof. Temperatures are given in degrees Celsius unless otherwise indicated.

EXAMPLE 1

In Vitro Cytotoxicity of Potentiating Agents in Chinese Hamster Ovary Cells

Chinese hamster ovary (CHO) tissue culture cells were obtained from Dr. Vic Ling, Princess Margaret Hospital, Toronto, Canada. The parental cell line (AuxB1) and a multidrug resistant line (C5S32) having an amplified form of the MDR drug transport protein were plated into 96-well microtitre culture dishes at 250 or 500 cells per well in minimal essential medium, type alpha, 10% fetal calf serum and incubated in 95% oxygen/5% carbon dioxide for 48 hours. After this period, the medium was changed and one-half of the culture was treated with Actinomycin D (Act D) (0.01 μM for AuxB1 cells and 0.5 μM for C5S32 cells). C5S32 cells are about 200-fold resistant to Actinomycin D compared to the parental AuxB1 cell line. In addition to Act D some of the cultures also received a dose of the potentiating agent at 0.1 to 5.0 μM. Thus, four conditions were tested in each screening assay: untreated cells in medium alone, cells receiving Act D alone, cells incubated with the potentiating agent alone, and cells incubated with a combination of Act D and the potentiating agent. Both the parental and mdr cell lines were treated with these four conditions simultaneously. Each experimental condition reported below is based on the average absorbance from eight replicate samples. The incubation with Act D and the test drug continued for 96 additional hours, after which 0.5 mg/ml MTT dye was added to the cultures and allowed to incubate for three hours.

The cells were solubilized by addition of DMSO and the absorbance at 570 nm was monitored. The absorbance is directly related to the number of surviving cells in the culture dish.

In Table 1 below, the absorbance was normalized so that cytotoxicity of the potentiating agent could be evaluated. Untreated cultures were given a value of 1.00 and the cultures receiving 0.1 to 5.0 μM of the potentiating agent are reported as a fraction of this value. To evaluate the compounds for inducing synergism with Actinomycin D, the absorbance values of cultures receiving Act D alone were assigned a value of 1.00 and cultures receiving the combination of Act D and potentiating agent Act D are reported as a fraction of this control. In most experiments, this concentration of Act D gave a reduction in cell number 10-20% below the value of completely untreated cultures.

TABLE 1

In Vitro Cytotoxicity of Potentiating Agents in Chinese Hamster Ovary Cells

Compound	Dose	Wildtype AUXB1		Drug Resistant C5S32	
		0	+ACT D	0	+ACT D
(A)	0.1 μM	1.114	1.105	1.037	0.927
	0.5 μM	0.926	0.730	0.978	0.453
	1.0 μM	0.970	0.471	0.759	0.283
	5.0 μM	0.015	0.035	0.016	0.022
(AC)	0.1 μM	0.938	0.852	0.921	0.697
	0.5 μM	1.260	0.782	0.997	0.340
	1.0 μM	1.109	0.706	0.952	0.247
	5.0 μM	1.207	0.176	1.036	0.021
(AK)	0.1 μM	0.997	0.967	1.048	0.923
	0.5 μM	1.047	0.564	1.069	0.373
	1.0 μM	0.968	0.499	1.139	0.094
	5.0 μM	1.111	0.092	1.068	0.023

EXAMPLE 2

In Vitro Cytotoxicity of Potentiating Agents in Human KB Epidermoid Carcinoma Cells

The procedure for assaying the cytotoxicity of potentiating agents with human KB epidermoid carcinoma cells is essentially the same as the assay procedure described above for use with Chinese hamster ovary cells. In brief, KB 3-1 (wt) and KB V-1 (mdr) cells are plated at 500 cells/well in 96-well culture plates in Dulbecco's modified eagle medium, supplemented with 10% fetal calf

serum. After 48 hours of incubation at 37°C, the media is changed and cells are treated with actinomycin D at 0.1 nM (3-1) or 20 nM (V-1). The test potentiating agent is introduced to one-half the untreated cultures and one-half the Act D treated cultures at 0.1 to 5.0 μM. After 96 hours of additional incubation at 37°C, 0.5 mg/ml MTT dye is added, the cells are incubated for three hours, after which the cells are dissolved in DMSO, and the absorbance is then read at 570 nm. The data is given in Table 2 below.

TABLE 2

In Vitro Cytotoxicity of Potentiating Agents in Human KB Epidermoid Carcinoma Cells

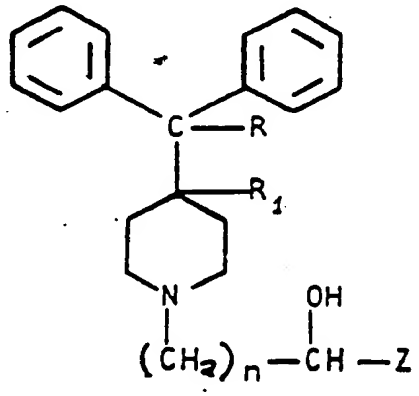
Compound	Dose	Wildtype KB 3-1		Drug Resistant KB V-1	
		0	+ACT D	0	+ACT D
(A)	0.1 μM	1.177	0.955	1.243	0.962
	0.5 μM	1.084	0.866	0.923	0.563
	1.0 μM	0.845	0.747	0.683	0.308
	5.0 μM	0.036	0.059	0.037	0.041
(AC)	0.1 μM	1.103	0.994	1.054	0.765
	0.5 μM	1.241	0.964	0.883	0.548
	1.0 μM	1.232	0.995	0.819	0.271
	5.0 μM	0.810	0.824	0.742	0.057
(AK)	0.1 μM	1.014	0.990	1.225	0.959
	0.5 μM	1.006	0.961	1.063	0.382
	1.0 μM	0.869	0.935	0.937	0.132
	5.0 μM	0.320	0.460	0.156	0.041

The foregoing examples are illustrative of the present invention, and are not to be taken as restrictive

thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

THAT WHICH IS CLAIMED IS:

1. A method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is harbored in a subject and which tumor is resistant to said antineoplastic agent, comprising concurrently administering to said subject an antineoplastic agent and a potentiating agent, said potentiating agent selected from the class consisting of



(I)

wherein

R represents hydrogen or hydroxy;

R_1 represents hydrogen; or

R and R_1 taken together form a second bond between the carbon atoms bearing R and R_1;

n is a positive whole integer of from 1 to 3;

Z is selected from the group consisting of thienyl, phenyl or substituted phenyl wherein the substituents on the substituted phenyl may be attached at the ortho, meta, or para positions of the substituted phenyl ring and are selected from the group consisting of a halogen atom, a straight or branched lower alkyl chain of from 1 to 4 carbon atoms, a lower alkoxy group of from 1 to 4 carbon atoms, a di(lower)alkylamino group, or a saturated monocyclic heterocyclic group selected from the group consisting of pyrrolidino, piperidino, morpholino, and N-(lower)alkylpiperazino,

and the pharmaceutically acceptable salts thereof,

said potentiating agent being administered in an amount effective to increase the sensitivity of said tumor to said antineoplastic agent.

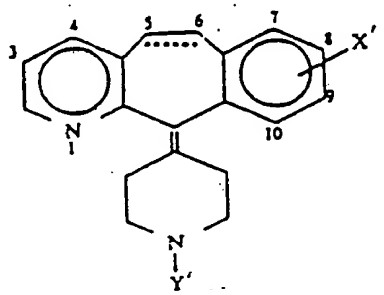
2. A method according to Claim 1, wherein said antineoplastic agent is administered to said subject parenterally and said potentiating agent is administered to said subject parenterally.

3. A method according to Claim 1, wherein said antineoplastic agent is selected from the class consisting of vinca alkaloids, epipodophyllotoxins, anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, taxol, colchicine, cytochalasin B, emetine, maytansine, and amsacrine.

4. A method according to Claim 1, wherein said tumor cells are adenocarcinoma cells.

5. A method according to Claim 1, wherein said compound is terfenadine.

6. A method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is harbored in a subject and which tumor is resistant to said antineoplastic agent, comprising concurrently administering to said subject an antineoplastic agent and a potentiating agent, said potentiating agent selected from the class consisting of



(II)

wherein the dotted line represents an optional double bond;

X' is hydrogen or halo; and

Y' is H, -COOR', or SO_2R',

with the proviso that when Y' is -COOR', R' is C1 to C12 alkyl, substituted C1 to C12 alkyl, phenyl, substituted phenyl, C7 to C12 phenylalkyl, C7 to C12 phenyl alkyl wherein the phenyl moiety is substituted or R' is -2,-3, or -4 piperidyl or N-substituted piperidyl wherein the substituents on said substituted C1 to C12 alkyl are selected from amino or substituted amino and the substituents on said substituted amino are selected from C1 to C6 alkyl, the substituents on said substituted phenyl and on said substituted phenyl moiety of the C7 to C12 phenyl alkyl are selected from C1 to C6 alkyl and halo, and the substituent on said N- substituted piperidyl is C1 to C4 alkyl;

and with the proviso that when Y' is SO_2R', R' is C1 to C12 alkyl, phenyl, substituted phenyl, C7 to C12 phenyl alkyl, C7 to C12 phenyl alkyl wherein the phenyl moiety is substituted, wherein the substituents on said substituted phenyl and said substituted phenyl moiety of the C7 to C12 phenylalkyl are selected from C1 to C6 alkyl and halo;

and the pharmaceutically acceptable salts thereof,

said potentiating agent being administered in an amount effective to increase the sensitivity of said tumor to said antineoplastic agent.

7. A method according to Claim 6, wherein said antineoplastic agent is administered to said subject parenterally and said potentiating agent is administered to said subject parenterally.

8. A method according to Claim 6, wherein said antineoplastic agent is selected from the class consisting of vinca alkaloids, epipodophyllotoxins, anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, taxol, colchicine, cytochalasin B, emetine, maytansine, and amsacrine.

9. A method according to Claim 6, wherein said tumor cells are adenocarcinoma cells.

10. A method according to Claim 6, wherein said compound is selected from the class consisting of:

(AC) 11-(N-Carboethoxy-4-piperidylidene)-6, 11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

(AD) 11-(N-Carboethoxy-4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

(AE) 11-(N-Carbomethoxy-4-piperidylidene)-6, 11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

(AF) 11-(N-Carbophenoxy-4-piperidylidene)-6, 11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

(AG) 11-(N-Carboisopropoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta- [1,2-b] pyridine;

(AH) 11-(N-Carbo-t-butoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

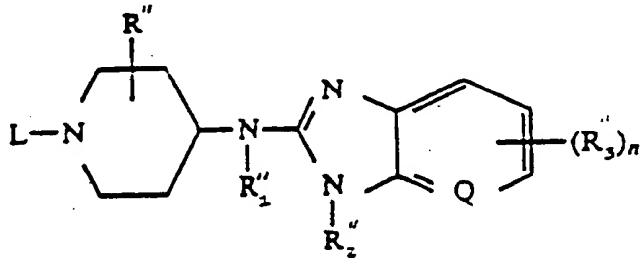
(AI) 11-(N-Methanesulfonyl-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine; and

(AJ) 11-(4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine;

and the pharmaceutically acceptable salts thereof.

11. A method according to Claim 1, wherein said compound is 11-(N-Carboethoxy-4-piperidylidene)-6, 11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine.

12. A method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is harbored in a subject and which tumor is resistant to said antineoplastic agent, comprising concurrently administering to said subject an antineoplastic agent and a potentiating agent, said potentiating agent represented by the formula:



(III)

and the pharmaceutically acceptable acid addition salts thereof, wherein

R'' is a member selected from the group consisting of hydrogen and lower alkyl;

R_1'' is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R_2'' is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono and diaryl(lower alkyl);

R_3'' is a member independently selected from the group consisting of halo, lower alkyl, lower alkyloxy and trifluoromethyl;

n'' is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and

L is a member selected from the group consisting of lower alkyl, which is optionally

substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; lower alkenyl; aryllower alkenyl; cycloalkyl, being optionally substituted with a cyano and/or an aryl group; 1-(aryllower alkyl)-1H-benzimidazol-2-yl; and a radical of the formula $Z''-C_mH_{2m}-$, wherein

m is an integer of from 1 to 6 inclusive; and

Z'' is a member selected from the group consisting of 4,5-dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted in its 4-position by an aryl radical or a lower alkyl radical; 2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzodioxin-6-yl; 2,3-dihydro-2-oxo- 1H-benzimidazol-1-yl; 2,3-dihydro-3-oxo-4H- benzoxazin-4-yl; (10,11-dihydro-5H-di-benzo[a,d]cyclohepten-5-ylidene)methyl; 4-morpholinyl; 1-piperidinyl; 1-pyrrolidinyl; a radical of the formula $T-N(R_4'')-$, wherein

R_4'' is a member selected from the group consisting of hydrogen, lower alkyl and aryllower alkyl; and

T is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, 1H-benzimidazol-2-yl; and

a radical of the formula

$$W - \overset{O}{\overset{\|}{C}} - (X'')_5 -$$

wherein

s is the integer 0 or 1;

X'' is a member selected from the group consisting of O and $-N(R_{5''})-$, said R5'' being a member selected from the group consisting of hydrogen, lower alkyl, aryllower alkyl, lower alkanoyl and aroyl; and

W is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, amino, arylamino, mono- and di(lower alkyl)amino, mono- and di(aryllower alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono-and di(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substitutents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono-and di(lower alkyl)amino, lower alkanoyl, a radical of the formula $R_{6''}-C_pH_{2p}-O-$, wherein

p is an integer of from 1 to 6 inclusive; and

$R_{6''}$ is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and a radical of the formula $R_{7''}-O-$, wherein

$R_{7''}$ is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower

alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di(lower alkyl)aminocarbonyl;

wherein said phenyl in the definition of said R_7'' may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy; and

wherein said aroyl in the definition of said L represents arylcarbonyl wherein said aryl is as defined hereabove,

said potentiating agent being administered in an amount effective to increase the sensitivity of said tumor to said antineoplastic agent.

13. A method according to Claim 12, wherein said antineoplastic agent is administered to said subject parenterally and said potentiating agent is administered to said subject parenterally.

14. A method according to Claim 12, wherein said antineoplastic agent is selected from the class consisting of vinca alkaloids, epipodophyllotoxins, anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, taxol, colchicine, cytochalasin B, emetine, maytansine, and amsacrine.

15. A method according to Claim 12, wherein said tumor cells are adenocarcinoma cells.

16. A method according to Claim 12, wherein said compound is astemizole.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/02248

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 45/06 A 61 K 37/02 //(A 61 K 37/02 A 61 K 31:445)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	Agents and Actions, vol. 18, nos 5-6, 1986, (Basel, CH), L.C. IORIO et al.: "Interaction studies in mice of SCH 29851, a potential non-sedating antihistamine, with commonly used therapeutic agents", pages 485-493, see abstract -----	1-16

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
08-04-1992	28. 04. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-16 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

As formulas I,II and III and the term "neoplastic agent" covers too many components, the search has been performed on the general idea and active agents mentioned in the ./.

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

examples of the description

Claims searched incompletely 1 - 16